Hydroxycarbamide: interstitial lung disease

● An analysis of 41 French reports of interstitial lung disease, including fibrosis, attributed to *hydroxycarbamide* (hydroxyurea), showed that onset occurred after a period varying from a few months to several years, and sometimes had a fatal outcome.

Hydroxycarbamide, alias *hydroxyurea,* is a cytotoxic drug administered orally in some myeloproliferative syndromes, and to some patients with sickle cell disease to prevent acutely painful vaso-occlusive crises, acute chest syndrome and hospitalisation (1-3). It carries the risks common to all cytotoxics, particularly leukopenia and (sometimes severe) thrombocytopenia, cutaneous and gastrointestinal disorders, and possibly cancer (1-4).

Three French regional pharmacovigilance centres analysed 41 cases of non-infectious pulmonary disease attributed to *hydroxycarbamide*, recorded in the French pharmacovigilance database between 1988 and 2019. The patients, male and female in similar numbers, were aged 49 to 91 years, with a median age of 77 years (5).

Half of the patients were taking *hydroxycarbamide* at a dose of less than 1 g/day. *Hydroxycarbamide* was used mainly for essential thrombocythaemia (13 cases), polycythaemia vera (11 cases), chronic myeloid leukaemia (4 cases), and myelofibrosis (4 cases). In 6 cases, the condition warranting administration of this drug was not stated (5).

The symptoms reported were dyspnoea (23 cases) with hypoxia in 11 cases, fever (17 cases), and cough (11 cases). The reported lung pathologies were interstitial lung disease (24 cases), pulmonary fibrosis (13 cases), and bronchiolitis obliterans organising pneumonia, BOOP (4 cases) (5,6).

The lung disorders appeared after taking *hydroxycarbamide* for a duration varying from 9 days to 14 years, with a median duration of 18 months. The median time to onset was 3 months for organising pneumonia, 15 months for interstitial lung disease and 41 months for fibrosis.

Of the 30 patients who stopped taking *hydroxycarbamide*, 15 recovered, 4 had a reduction in symptoms and 3 died, while the outcome for the other 8 is not known. Of the 4 patients who continued to take *hydroxycarbamide*, 2 died, 1 recovered, and the outcome for the fourth is not known. For 8 patients, it is not known whether the drug was stopped or continued. In 6 patients, reintroduction of *hydroxycarbamide* was followed by a reappearance of the disorders (5).

There seem to be two types of lung disease: acute interstitial lung disease with fever; and chronic non-febrile lung disease with fibrosis and a later time of onset.

As of late 2021, interstitial lung disease, including fibrosis, is mentioned in the French summary of product characteristics (SPC) for the proprietary drug based on *hydroxycarbamide* which is authorised for use in myeloproliferative syndromes (2).

However, the European SPCs for brands based on *hydroxycarbamide* which are authorised in sickle cell disease (Siklos°, Xromi°) do not mention any lung disorders, despite the use of dosages similar to those used in myeloproliferative syndromes (2,3). As of 17 January 2022, the publicly accessible section of the European pharmacovigilance database lists a few reports of dyspnoea, but the extent to which they were related to anaemia or to lung disease is not known (7).

Act early, if possible before the onset of fibrosis. It is important to rapidly recognise the signs suggestive of interstitial lung disease due to *hydroxycarbamide*. If *hydroxycarbamide* is discontinued at an early stage, the disorder will often regress.

It is particularly important to report the occurrence of interstitial lung disease associated with *hydroxycarbamide* in a patient with sickle cell disease.

► Translated from *Rev Prescrire* March 2022 Volume 42 N° 461 • Page 194

Selected references from Prescrire's literature search

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5- Ginisty S "Hydroxyurea-Induced Pneumopathy: Study in the French Pharmacovigilance Database" *Fundam Clin Pharmacol* 2021; **35** (suppl 1): 160-161 (abstract PS-144: full article 1 page).

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